REMARKS

A check for $465 for the fees for a three-month extension of time accompanies this response. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 50-1213.

In compliance with our duty of disclosure, the Examiner's attention is directed to co-pending U.S. application Serial Nos. 09/905,501, 10/317,269 and 10/410,700, and allowed U.S. application Serial No. 09/271,575, now U.S. Patent No. 6,602,274. The named inventor of the instant case is the same named inventor of the patent and all of the listed applications. In light of the allowance of the claims in U.S. application Serial No. 09/271,575, and absent some intervening art, it is respectfully submitted that the instantly pending claims should be novel and unobvious. It is noted that if any rejections for obviousness-type double patenting are initiated, then any Action with such rejection cannot be made final.

In the specification, new paragraph [000.1] is added to correct a typographical/formatting error that occurred when the original specification was re-typed into paragraph format from page/line number format and submitted as a substitute specification on October 31, 2001. The RELATED APPLICATIONS paragraph was inadvertently omitted. This amendment reintroduces into the replacement specification the material found on page 1, lines 1-8 of the original specification. Paragraphs [021] and [042] are amended herein to correct typographical errors, basis for which is found in the specification (for example, see paragraphs [061] and [064]. Paragraph [061] is amended to delete a duplicated word and to correct a minor grammatical error.

Claims 1-6, 11, 12, 16-24, 36 and 38-41 are presently pending in this application. Claims 7-10, 13-15, 25-35 and 37, which are drawn to non-elected subject matter, are cancelled herein without prejudice or disclaimer. Applicant

Claim 1 is amended to include the recitation "wherein a combination of an intensity of light used for the step of illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged." Basis for the amendment is found throughout the specification (for example, see paragraphs [014] and [015] on page 5 and paragraph [032] on page 9). Claim 1 and claims 4 and 18-22 are amended to correct a minor grammatical error, replacing the noun "neovasculature" with the adjective "neovascular."

Claims 2, 3, 23 and 24 are amended to more distinctly claim the subject matter, basis for which is found in the specification (for example, see paragraph [013]. Claims 23 and 24 are further amended to correct dependency, as the claims depend from claim 2. Claim 11 is amended to more distinctly claim the subject matter by replacing the term "bindable pair" with the term "binding pair," basis for which is found in the specification (for example, see paragraph [009]. Claim 11 is also amended to correct minor grammatical errors.

Basis for new claim 38 can be found throughout the specification (for example, see paragraph [042] on pages 11 and 12). Basis for new claim 39 can be found throughout the specification (for example, see paragraph [058] on page 16). Basis for new claim 40 can be found throughout the specification (for example, see paragraph [042] on pages 11 and 12). Basis for new claim 41 can be found throughout the specification (for example, see paragraph [040] on page 11). No new matter is added nor are any amendments made to change the scope of the claims.

INFORMATION DISCLOSURE STATEMENT OF APRIL 8, 2002

The Examiner alleges that the Information Disclosure Statement, filed on April 2, 2002, is defective because references A-DZ were allegedly not [illegible] respectfully disagrees. Copies of the

are attached herewith in the Appendix as evidence that the references were

included in the original submission and were delivered to and received by the Office on April 8, 2002. The applicant's representative spoke with the Examiner by telephone on March 12, 2003, and explained that five volumes of references, contained in two boxes, were hand-delivered to the Office on April 8, 2002. At that time, the Examiner stated that attempts would be made to locate the references. The applicant's representative telephoned the Examiner again on July 21, 2003, to determine whether the missing references had been located. The Examiner stated that a "trace" would be initiated to locate the boxes containing the references.

The applicant respectfully requests that the Examiner accept the attached PTO-1449 as a replacement copy, locate the boxes containing the cited references, and consider the art supplied in the Information Disclosure Statement filed on April 8, 2002, and enter this Information Disclosure Statement into the file history of this application.

NAMED INVENTOR

In paragraph 14 on page 10 of the Office Action mailed February 25, 2003, the Examiner indicates that this application currently names joint inventors. Applicant respectfully submits that James Chen is the only named inventor of this application.

THE PENDING CLAIMS

Claims 1-6, 11, 12, 16-24 and 36 are restricted into 24 groups (Groups I through XXIV) based upon limitations in the dependent claims. Each of claims 1-6, 11, 12, 16-24 and 36, however, is directed to a generic method for treating neovascular disease of the eye. If the claims are divided as required by the Examiner, it never will be possible to get a generic claim, such as claim 1, examined or issued. There are no reasons of record to establish that the generic claims should not be examined and issued. Nevertheless, no group of the

encompass the generic methods as set forth. Thus

precludes applicant from prosecuting and obtaining such claims.

Furthermore, the Examiner's attention is directed to MPEP §809.03, which states:

> There are a number of situations which arise in which an application has claims to two or more properly divisible inventions, so that a requirement to restrict the application to one would be proper, but presented in the same case are one or more claims (generally called "linking" claims) inseparable therefrom and thus linking together the inventions otherwise divisible.

MPEP §809.03 defines one type of linking claim as a genus claim linking species of the genus. Claims 1-6, 11, 12, 16-24 and 36 as filed are generic claims and hence are linking claims, linking each of the groups into which the claims have been restricted. Each of these claims links Groups I-XXIV. For example, Claim 1 is restricted into each of Groups I through XXIV, yet none of the groups singly or in combination of all of them includes the generic method of claim 1. As linking claims, claims 1-6, 11, 12, 16-24 and 36 should be examined with the elected group. According to MPEP§809:

> The linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn. Any claim(s) directed to nonelected inventions(s), previously withdrawn from consideration, which depends from or includes all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability. Where such withdrawn claims have been canceled by applicant pursuant to the restriction requirement, upon allowance of the linking claim(s), the Examiner must notify applicant that any canceled, nonelected claim(s) which depends from or includes all the limitations of the allowable linking claim may be reinstated by submitting the claims in an amendment. Upon entry of the amendment, the amended claim(s) will be fully examined for patentability.

Thus, because claims 1-6, 11, 12, 16-24 and 36 are linking claims that link more than one group, the linking claims **must** be examined with the elected group; if the linking claims are deemed allowable, then the restriction requirement must be withdrawn and all claims directed to nonelected subject

must be rejoined. Accordingly, applicant's retained nonelected claims

16-24 and 36 in their present form in the application, pursuant to MPEP §809.04.

REJECTION OF CLAIMS 1-6, 11-12, 16-24 and 36 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH - SCOPE

Claims 1-6, 11-12, 16-24 and 36 are rejected because the specification allegedly provides insufficient guidance as to (1) the structure or function of the targeted photosensitizing compound; (2) the structure or function of the binding pair; (3) how the photosensitizing compound is bound to the binding pair; (4) the specific ligand or receptor of the binding pair; (5) the "first component" and "second component" of any undisclosed binding pair because the term "component" allegedly "could be as little as one amino acid or it could be as much as 100 amino acids"; (6) the structure or function of an antigen, receptor or ligand on abnormal endothelium; (7) the antigen on the abnormal endothelium that is being targeted; and (8) whether any of the undisclosed ligands, receptors or antigens are expressed on neovasculature of abnormal endothelium.

The Examiner states that the specification is enabling for the method to treat neovascular disease of the eye including administering a targeted photosensitizing compound such as verteporfin conjugated to L19 antibody that binds to the ED-B domain of fibronectin, and benzoporphyrin conjugated to VEGF that selectively binds to abnormal endothelium that lines or composes neovascular tissue and illuminating the neovasculature tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue but without impairing or destroying other tissue, but alleges that the specification does not reasonably provide enablement for

1) a method to treat any neovascular disease of the eye including administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue

2) the method where the light is non-laser light, laser light, light

degeneration or diabetic retinopathy,

4) the method where the targeted photosensitizing compound is bound to *any* first component of *any* bindable pair and wherein *any* second component of *any* bindable pair is selected from the group consisting of *any* receptor present on abnormal endothelium, *any* antigen present on abnormal endothelium, and *any* antibody bindable to *any* antigen on abnormal endothelium

5) the method where the targeted photosensitizing compound is bound to *any* first component of *any* bindable pair and wherein *any* second component of *any* bindable pair is selected from the group consisting of *any* receptor present on abnormal endothelium, *any* antigen present on abnormal endothelium, and *any* antibody bindable to *any* antigen on abnormal endothelium where the targeted photosensitizing compound is incorporated into a liposomal preparation

6) the method to treat any neovascular disease of the eye including administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue where the targeted photosensitizing compound is bound to *any* bi-specific antibody construct that includes both *any* ligand component and *any* receptor component

7) the method to treat any neovascular disease of the eye including administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue where the targeted photosensitizing compound is bound to any bi-specific antibody construct that further comprises both any ligand component and any receptor component where the targeted photosensitizing compound is incorporated into a liposomal preparation

8) the method to treat any neovascular disease of the eye including administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue where the photosensitized neovasculature is illuminated for 4 minutes, 20 minutes, 1 hour or 24 hours

9) the method where the neovasculature is treated with a total fluence of light irradiation from between 240 J/cm^2 to about 900 J/cm^2

10) the method of instructing any person to treat any neovascular disease of the eye including instructing any person to conduct a method to treat any neovascular disease of the eye including administering *any* targeted photosensitizing compound which

tumor of malignant uveal melanomas

The Examiner alleges that no guidance on how any methods other than those specifically exemplified can be used in a method to treat neovascular disease of the eye, and argues that "given the indefinite number of photosensitizing compounds, antigens, bindable pairs or any ligand or receptor, antibody to ligand, antibody to receptor and whether the undisclosed ligand, receptor or antigen are expressed on neovasculature of abnormal endothelium, it is unpredictable which undisclosed ligand, receptor, antigen, and antibody to the ligand or receptor would be effective for targeting the photosensitizing compound to the abnormal endothelium as a method to treat neovascular disease of the eye." Hence, the Examiner states that the disclosed steps are enabled but are allegedly not commensurate in scope with these claims. The Examiner concludes that one of skill in the art would not be able to practice the claimed methods without an undue amount of experimentation.

This rejection is respectfully traversed.

RELEVANT LAW

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176

The "invention" referred to in the enablement requirement of section 112 is the claimed subject matter. *Lindemann Maschinen-fabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984) ("The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention"); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835, 225 USPQ 232 (1984).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with evidence or reasoning which is inconsistent with the contested statement.

Id. (emphasis in original); *See also Fiers v. Revel*, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, *Gould v. Mossinghoff*, 229 USPQ 1, 13 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. § 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct"). A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible if it is routine or if the specification contains a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. The amount of experimentation that is permissible depends upon a number of factors, such

include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The PTO has promulgated guidelines, which incorporate the above-noted law, for examining chemical/biotechnical applications with respect to 35 U.S.C. §112, first paragraph, enablement. As set forth in the guidelines, the standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988). In determining whether any experimentation is "undue," consideration must be given to the above-noted factors.

As indicated in the published guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. The focus of the inquiry is whether everything within the scope of the claim is enabled. As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to

claimed invention without undue experimentation.

It is incumbent upon the Examiner to first establish a *prima facie* case of non-enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim ... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

ANALYSIS

The Office Action fails to establish a *prima facie* case of lack of enablement pursuant to 35 U.S.C. § 112, first paragraph.

It would not require undue experimentation to use the claimed methods in the treatment of neovascular disease of the eye

As discussed below, the claims are commensurate in scope with the disclosure, which exemplifies particular embodiments within the scope of the claims and teaches how one of skill in the art can practice other embodiments within the scope of the claims. In particular, there is a substantial amount of guidance presented in the specification, the level of skill in the art is high, there

photodynamic therapy are provided in the specification and are known to the

skilled artisan, as discussed in detail below, and any necessary adjustment can be determined empirically using routine testing or even based on theoretical calculations. Having taught the requisite result to be achieved — a method to treat neovascular disease of the eye that includes administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovasculature tissue where a combination of an intensity of light used for the step of illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the target tissue is destroyed and the non-target tissue through which the light passes remains undamaged— it would not require undue experimentation to select appropriate conditions to achieve the desired result. Thus, it would not require undue experimentation for one of skill in the art to make and use the claimed subject matter.

Evaluation of the above Factors

1. The scope of the claims

Claim 1 is directed to a method to treat neovascular disease of the eye that includes administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovasculature tissue, and illuminating the neovasculature tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue but without impairing or destroying other tissue, where a combination of an intensity of light used for the step of illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Claims 2-6, 11-12, 16-24 and 36 all ultimately depend from claim 1 and are directed to various embodiments. Claims 2 and 3 are directed to the method of claim 1 where the light is non-coherent or coherent, respectively. Claim 4 is directed to the method of claim 1 where the neovasculature tissue is present in retina, choroid,

Claim 11 is directed to the method of claim 1, where the targeted photosensitizing compound is bound to a first member of a binding pair and where a second member of the binding pair is selected from the group consisting of a receptor present on abnormal endothelium; a ligand bindable to receptor present on abnormal endothelium; an antigen present on abnormal endothelium; and an antibody bindable to antigen present on abnormal endothelium. Claim 12 is directed to the method of claim 11, wherein the targeted photosensitizing compound is incorporated into a liposomal preparation. Claim 16 is directed to a method of claim 1 where the targeted photosensitizing compound is bound to a bi-specific antibody construct that further includes both a ligand component and a receptor component. Claim 17 is directed to the method of claim 16 where the targeted photosensitizing compound is incorporated into a liposomal preparation.

Claims 17, 18, 19 and 20 are directed to embodiments of claim 1 where the neovasculature is illuminated for at least 4 minutes, 20 minutes, 1 hour and 24 hours, respectively. Claim 22 is directed to the method of claim 1, where the neovasculature tissue is treated with a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2. Claims 23 and 24 are directed to embodiments of claim 2 where the non-coherent light source is a light emitting diode and ambient light, respectively. Claim 36 is directed to a method of instructing a person to treat neovascular disease of the eye, comprising instructing a person to conduct a method according to claim 1.

2. Level of skill in the art

In this instance, the level of skill in the art is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and

other evidence the high level of skill in this art [illegible] fact the prior art indicates

that the first use of photodynamic therapy was in 1966 (T. J. Dougherty, *Seminars in Surgical Oncology* 2:24-37 (1986)), and that studies in the 1970s and 1980s were directed to using porphyrins and chlorins for treatment of hyperproliferative and neoplastic vascular tissue (Williams *et al.* (U.S. 5,576,013; 1996). The age of the cited art is a strong factor supporting the view that the skilled artisan would have been familiar generally with use of photosensitizing compounds in photodynamic therapy for treatment of neovascular tissues. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

3. State of the Art

At the time of filing of the instant application, a broad body of knowledge had amassed in the areas of pharmaceutical sciences, medicine, and biochemistry directed to the use of photodynamic therapy as a treatment for hyperproliferative tissues. Many of these articles and patents have been made of record in this application. In addition, Pandey *et al.* (*J Molecular Recognition* 9:118-122(1996)) discloses that photodynamic therapy is "a well recognized treatment for the destruction of tumors which utilizes the ability of a selectively retained photosensitizer to elicit an efficient photodynamic reaction upon activation with light." Many photosensitizing compounds were known at the time the application was submitted, including hematoporphyrins, porphyrins, chlorins, bacteriochlorins, benzoporphyrins, phthalocyanines, metallo-phthalocyanines and purpurines and their derivatives; naphthalocyanines, texaphyrins, porphycenes, platyrins and other extended tetrapyrroles (Kreimer-Birnbaum, *Sem Hematol. 26(2)*: 157-173 (1989)). Richter *et al.* (U.S. Patent No. 5,770,619) discloses photosensitizing compounds including merocyanines, pheophorbides, psoralens, monoaspartyl chlorin, zinc phthalocyanine, tin etiopurpurin and porfimer sodium, and pro-drugs such as δ-aminolevulinic acid which can produce drugs such as protoporphyrin in tissue. Additional PDT

1988). Other known PDT agents include pyrromethane boron difluorides, indocyanine green, zinc phthalocyanine, rose bengal, epigallocatechin, epicatechin derivatives, hypocrellin B, urocanic acid, indoleacrylic acid, rhodium complexes, etiobenzochlorins, octaethylbenzochlorins, sulfonated Pc-naphthalocyanine, chloroaluminum sulfonated phthalocyanine, iminium salt benzochlorins and other iminium salt complexes, Merocyanin 540, Hoechst 33258, acridine compounds, suprofen, tiaprofenic acid, furocoumarin hydroperoxides, Victoria blue BO, methylene blue and toluidine blue (U.S. Patent No. 5,576,013 (Williams *et al.*, 1996)). Kessel *et al.* (*Photochemistry and Photobiology 58(2)*: 200-203 (1993) discloses assays useful as predictive of the efficiency of photosensitizing compounds in photodynamic therapy. Henderson *et al.* (Cancer Research 57: 4000-4007 (1997) teaches that tumor cell photosensitization, tumor response and vascular photosensitization are linked through common mechanisms.

The subject matter of claims 1-6, 11, 12, 16-24 and 36 is directed to methods of photodynamic therapy (PDT) to treat neovascular disease of the eye. PDT is a treatment that is based on the preferential uptake and selective retention of photosensitizing agents by hyperproliferative cells compared to normal cells (Kessel *et al.*, *Photochem Photobiology 58(2)*:200-203 (1993), page 200, first paragraph; Dougherty, *Seminars in Surgical Oncology 2*:24-37 (1986), page 24, first paragraph; and Pandey *et al.*, *J Molecular Recognition 9*: 118-122 (1996), page 118, first paragraph). Subsequent irradiation of the cells causes a photochemical reaction that is believed to generate chemically disruptive species, such as singlet oxygen, which disrupt or destroy the cell through reaction with cellular components or nuclear membranes (Rodgers *et al.*, U.S. Patent 6,071,944, col. 1, lines 18-25; and Weinstein *et al.*, U.S. Patent 4,753,958, col. 3, lines 9-38).

Chlorins and porphyrins have been used in photodynamic therapy as a treatment for diseases associated with hyperproliferation and neovascularization,

disease and age related macular degeneration ... neovascular ... tissue

Maturing Medical Technology, OE-Reports, No. 194, February 2000, page 3, paragraphs 2 and 5). Neovascularizations are occluded using chlorins in PDT methods (Schmidt-Erfurth *et al.*, *Lasers in Surgery and Medicine* 17: 178-88 (1995)). Many photosensitizing agents including benzoporphyrin derivatives, dihematoporphyrin, hematoporphyrin, porphyrin derivatives, indocyanines and phthalocyanines have been used to induce photothrombosis within target vascular tissue (Williams *et al.*, U.S. Patent No. 5,576,013 (1996)).

These references to numerous published protocols for photodynamic therapy, the identification, production and/or extraction of photosensitizing agents, and the use of such compounds to treat a variety of hyperproliferative tissues including neovascular tissue demonstrate the large volume of information regarding tested and reliable procedures available at the time of filing of the application, and thus evidence the state of the art at the relevant time.

4. Teachings in the Specification and Presence of Working Examples

Structure or Function of Photosensitizing Compound

The Examiner alleges that the specification provides insufficient guidance as to the structure and function of the photosensitizing compound. The applicant respectfully disagrees. The specification provides a detailed amount of direction and guidance for selection of a photosensitizing compound that is encompassed in the claims. For example, paragraph [036] discloses that

> a photosensitizing compound is a chemical compound which homes to one or more types of selected target cells and, when contacted by radiation, absorbs the light, which results in impairment or destruction of the target cells. Virtually any chemical compound that homes to a selected target and absorbs light may be used in this invention. Preferably, the chemical compound is nontoxic to the subject to which it is administered or is capable of being formulated in a nontoxic composition. Preferably, the chemical compound in its photodegraded form is also nontoxic.

The specification teaches that the function of the photosensitizing compound is

spectra of the photosensitizer (paragraph [005]), which results in impairment or

destruction of the target cells (paragraph [036]). The photosensitizing agent function in photodynamic therapy is well known to those skilled in the art (for example, see Dougherty *et al.*, *Proc. Int. Symp. Porphyrins Tumor Photother.*, Milan, 16-18 May 1983; Sternberg *et al.*, *Tetrahedron 54*: 4151-4202 (1998).

The Examiner alleges that the specification provides insufficient guidance as to the structure of the targeted photosensitizing compound. Applicant respectfully submits that the instant claims are not directed to any specific photosensitizing compound, but are directed to particular methods of using such compounds to treat neovascular disease of the eye. Therefore the structure of the photosensitizing compound is not relevant to patentability since any photosensitizing compound is contemplated for use in the claimed methods. The specification teaches that the photosensitizing compound absorbs light in the range of 500 nm - 1100 nm and that virtually any chemical compound that homes to a selected target and is activated by light may be used in the claimed method (see paragraph [036]). Further, the specification provides exemplary photosensitizing compounds, including any one or combination of chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD), porfimer sodium, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and pro-drugs such as δ-aminolevulinic acid, which can produce drugs such as protoporphyrin (see paragraph [036]), and pyropheophorbide compounds, bacteriochlorophyll derivatives, alkyl ether analogs of chlorins (see paragraph [040]).

The specification teaches the requisite properties for photodynamic therapy. For example, the specification teaches that the photosensitizing compounds have a light absorbance in a range of 500 to 1100 nm (paragraph [036]). The specification teaches methods of administering the photosensitizing compound (paragraph [046]). The specification teaches that the use level of the photosensitizing compound can be determined clinically (paragraph [047]) and

that the duration of illumination will be determined empirically but is preferably a total or cumulative period of time between 4 minutes and 148 hours (paragraph [048]). The specification also teaches that the total fluence of the light is between 30 Joules and about 25,000 Joules (see paragraph [049]) using an intensity of light substantially less that 500 mW/cm^2, where a combination of an intensity of light used for illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged (see paragraph [[050]). The specification teaches how to evaluate the effectiveness of the method in treating neovascular disease of the eye, such as standard visual acuity testing, ophthalmoscopy, color fundus photography and stereo fluorescein angiography (see paragraphs [053] and [057]).

The specification provides several working examples illustrating exactly how to use various photosensitizing compounds in the claimed methods for treating neovascular disease of the eye. Specifically, EXAMPLE 1 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound verteporfin conjugated to a bindable fragment of the L19 antibody demonstrating high affinity to the ED-B of fibronectin in a method to treat choroidal neovasculature lesions (see paragraphs [053] - [057]). EXAMPLE 2 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound a benzoporphyrin derivative conjugated to VEGF in a method to treat retinal neovasculature lesions (see paragraphs [058] through [060]). EXAMPLE 3 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound texaphyrin conjugated to antibody elicited to $\alpha v\beta 3$ in a method to treat vascular tumors of the eye (see paragraphs [061] and [062]). EXAMPLE 4 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound both texaphyrin conjugated to antibody elicited to $\alpha v\beta 3$ and a benzoporphyrin derivative conjugated to an

tumors of the eye (see paragraphs [063] through [066]).

Therefore, in light of the high level of skill in the art, the extensive teachings regarding photosensitizing compounds in the art, and the teachings of the specification, which provides at least 17 exemplars of photosensitizing compounds from various chemical classes, and which provides several working examples of photosensitizing compounds used in exemplary *in vivo* methods, it is respectfully submitted that it would not require undue experimentation for a skilled artisan to select and use a photosensitizing agent in the claimed methods.

Conjugating the Photosensitizer to the Binding Pair

As a preliminary matter, applicant respectfully submits that claims 1-6 and 16-24 do not include as subject matter a binding pair. The Examiner alleges that the specification does not teach how to use any claimed method because it is alleged that there is insufficient guidance as to how to bind a photosensitizing compound to the first member of a binding pair. The applicant respectfully submits that a patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). The techniques to construct conjugates of ligands with photosensitizers are well known to those of ordinary skill in this art. For example, Rakestraw *et al.* teaches conjugating a chlorin via covalent bonds to monoclonal antibodies (Rakestraw *et al.*, *Proc. Nat. Acad. Sci. USA 87*: 4217-4221 (1990). Sessler *et al.* (U.S. 5,994,535 (1999)) teaches conjugating texaphyrin to antibodies, proteins and site-specific transport molecules. Sternberg *et al.*(*Tetrahedron 54*: 4151-4202 (1998)) teaches conjugating porphyrins to biomolecules including antibodies, steroids, sugars, and polynucleotides. Fritzberg *et al.* (U.S. 5,976,535 (1999)) teaches conjugating cytotoxic agents to one member of a ligand/anti-ligand binding pair, and teaches conjugation to a receptor, an oligonucleotide, an enzymatic substrate or other binding site present on or in the target cell population. Richter *et al.* (U.S.

A variety of coupling agents, including cross-linking agents, can be used for covalent conjugation. Examples of cross-linking agents include N,N'-dicyclohexylcarbodiimide (DCC), N-succinimidyl-S-acetyl-thioacetate (SATA), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), ortho-phenylene-dimaleimide (o-PDM), and sulfosuccinimidyl 4-(N-maleimido-methyl)-cyclohexane-1-carboxylate (sulfo-SMCC). See, *e.g.*, Karpovsky *et al. J. Exp. Med. 160*: 1686 (1984); and Liu, MA *et al.*, *Proc. Natl. Acad. Sci. USA 82*: 8648 (1985). Other methods include those described by Brennan *et al.*, *Science 229*: 81-83 (1985) and Glennie *et al.*, *J. Immunol. 139*: 2367-2375 (1987). A large number of coupling agents, along with buffers, solvents, and methods of use, are described in the Pierce Chemical Co. catalog, pages O-90 to O-110 (1995).

Therefore, in light of the high level of skill in the art, and in light of the extensive teachings in the art of conjugating compounds such as photosensitizing agents to ligands and receptors, and the teachings of the specification, it is respectfully submitted that it would not require undue experimentation to bind a photosensitizing compound to the first member of a binding pair.

Structure and Function of the Binding Pair

The Examiner alleges that the specification provides insufficient guidance as to the structure and function of the binding pair to which the targeted photosensitizing compound is bound. Applicant respectfully submits that the instant claims are not directed to any specific binding pair, but submits that one embodiment is directed to a method to treat neovascular disease of the eye using targeted photosensitizer compounds conjugated to a binding pair. Thus, the structure of the binding pair is not relevant to patentability.

It is respectfully submitted that binding pairs were well known to those skilled in the art at the time the application was filed. Examples of ligand-receptor binding pairs are set out in U.S. Pat. Nos. 4,374,925 (Litman *et al.*,

hormones and hormone receptors ... steroids ... antibodies ...

and antigen pairs; enzymes and substrates, drug and drug receptor; cell-surface antigen and lectin; two complementary nucleic acid strands; nucleic acid strands and complementary oligonucleotides; interleukin and interleukin receptor; and stimulating factors and there receptors, such as macrophage colony stimulating factor (MCSF) and MCSF receptor. It is further submitted that conjugating binding pairs to photosensitizing compounds was also known to those of skill in the art at the time the application was filed (for example, see Fritzberg *et al.*, U.S. 5,976,535 (1999); Davalian *et al.*, U.S. 5,616,719 (1997); and Pease *et al.*, U.S. 5,618,732 (1997)). The instantly claimed binding pairs include those specific receptors and/or antigens present on abnormal endothelium and those specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens (see paragraph [014]).

The "function" of the binding pair is to allow selective binding or precise targeting of the photosensitizing compound to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens (see paragraphs [014] and [032]). The applicant respectfully submits that the requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples **or** by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973). The specification teaches a binding pair that includes a ligand bindable to a receptor present on abnormal endothelium and a receptor present on abnormal endothelium, and teaches another binding pair that includes an antibody bindable to antigen present on abnormal endothelium and an antigen present on abnormal endothelium (see paragraph [020]). The specification provides as specific examples of binding pairs a bindable fragment of the L19 antibody to the ED-B of fibronectin and the ED-B of fibronectin (paragraph [054]), VEGF and VEGF receptor (paragraphs [058] and [059]), integrin $\alpha v\beta 3$ and anti-integrin $\alpha v\beta 3$ antibody (paragraph [061]), and carcinoembryonic antigen (CEA) and anti-

Therefore, in light of the high level of skill in the art, and in light of the extensive teachings in the art on binding pairs and on conjugating compounds to binding pairs, and the teachings of the specification, which includes generic and specific examples of binding pairs, and provides working examples of exemplary binding pairs conjugated to photosensitizing compounds, it is respectfully submitted that it would not require undue experimentation to select a binding pair to which a photosensitizing compound can be conjugated to provide specific targeting to abnormal endothelium.

The Term "Component" in Claim 11

The Examiner alleges that the specification provides insufficient guidance as to the "first component" and "second component" of any undisclosed binding pair because the term "component" allegedly "could be as little as one amino acid or it could be as much as 100 amino acids." The applicant respectfully submits that amendment of claim 11 herein obviates this rejection.

Structure/Function of an Antigen, Receptor or Ligand

The Examiner alleges that the specification provides insufficient guidance as to the structure and function of an antigen, receptor or ligand on abnormal endothelium and alleges that it is thus unpredictable which undisclosed antigen, receptor or ligand would be effective for targeting a photosensitizing compound to abnormal endothelium. Applicant respectfully submits that none of claims 1-6, 11, 12, 16-24 and 36 is directed to any specific antigen, receptor or ligand on abnormal endothelium. The pending claims are directed to methods to treat neovascular disease of the eye. Claim 11 and its dependent claims include using a targeted photosensitizer compound conjugated to one member of a binding pair that targets an antigen, receptor or ligand on abnormal endothelium. Thus, the overall structure of the antigen, receptor or ligand is not relevant to patentability. Any antigen, receptor or ligand that appears on abnormal endothelium and can serve as a specific targeting moiety by which a targeted

It is respectfully submitted that various antigens, receptors and ligands on abnormal endothelium were well known to those skilled in the art at the time the application was filed. For example, known endothelial receptors at the time the application was filed include, among others, VEGF receptors and $\alpha v\beta 3$ integrins (see Ferrara, *Curr Top Microbiol Immunol*, 237:1-30, 1999; Elicieri *et al.*, *The Journal of Clinical Investigation*, 103:1227-30, 1999; and Smith *et al.*, *Br J Opthamol*, 83:486-494, 1999); the extra-domain B (ED-B) of fibronectin (Birchler *et al.*, *Nature Biotech.* 17:984 (1999)); endothelial-leukocyte adhesion molecule (ELAM-1), endoglin, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), the agent for leukocyte adhesion molecule-1 (LAM-1 agent), and HLA-DR, HLA-DP or HLA-DQ (Thorpe, U.S. Patent No. 5,855,866 (1999); and the selectins (or Lectin, EGF, Complement-Cellular Adhesion Molecules or LEC-CAMs) including L-Selectin (LECAM-1, LAM-1, gp90MEL), E-Selectin (LECAM-2, ELAM-1) and P-Selectin (LECAM-3, GMP-140, PADGEM) (Rao *et al.*, U.S. Patent No. 5,624,909 (1997)). The specification teaches as exemplary vascular endothelial receptors VEGF, $\alpha v\beta 3$ integrins and ED-B of fibronectin (see paragraphs [042], [054], [058], [061] and [064]). The specification also provides specific working examples of such targeting moieties (see paragraphs [054], [058], [061] and [064]).

The "function" of the antigens, receptors or ligands on abnormal endothelium is to allow selective binding or precise targeting of the photosensitizing compound to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens (see paragraphs [014] and [032]).

Therefore, in light of the high level of skill in the art, and in light of the extensive teachings in the art on antigens, receptors or ligands on abnormal endothelium, and the teachings of the specification, which includes generic and

submitted that it would not require undue experimentation to select an antigen, receptor or ligand on abnormal endothelium to which a photosensitizing compound can be specifically targeted to allow targeting of the photosensitizing compound to abnormal endothelium.

Antibody Binding Specificity

The Examiner alleges that, because the specific antigen, receptor or ligand is not disclosed in the specification, the binding specificity of the antibody is questionable, and alleges that the method is not enabled because without knowing the antibody binding specificity it is questionable whether the targeted photosensitizing compound would bind specifically to the undisclosed antigen on the abnormal endothelium. Applicant respectfully submits that none of the pending claims is directed to any specific antibody. Claim 11 is directed to a method of treating neovascular disease of the eye using targeted photosensitizer compounds conjugated to one member of a binding pair, where the binding pair is selected to include an antibody bindable to endothelial receptors and antigens. Thus, the overall structure of the antibody and its exact binding specificity is not pertinent to patentability. The antibody need only demonstrate the ability to combine specifically or have a high degree of affinity for abnormal endothelium when compared to its reactivity toward non-target tissue, so that the antibody can serve as a specific targeting moiety by which a photosensitizing compound conjugated to the antibody can selectively bind to abnormal endothelium.

The specification teaches that the antibody is selected to be bindable to endothelial receptors and antigens ([014]), and provides as examples antibody elicited to an antigenic determinant on abnormal endothelium, such as the extra domain B of fibronectin (paragraph [021]) and $\alpha v\beta 3$ integrins (paragraph [061]) or to antigen associated with choroidal tumor, such as carcinoembryonic antigen (paragraph [063]). Methods of making antibodies with specificity to abnormal endothelium were known at the time the application was filed (see Thorpe, U.S.

Therefore, in light of the high level of skill in the art, and in light of the extensive teachings in the art on antibodies having specificity to abnormal endothelium, and the teachings of the specification, which includes generic and specific examples of antibodies having specificity to abnormal endothelium, and which provides working examples of exemplary antibodies, it is respectfully submitted that it would not require undue experimentation to select an antibody having specificity to abnormal endothelium to which a photosensitizing compound can be conjugated to allow targeting of the photosensitizing compound to abnormal endothelium.

Expression of the Ligands, Receptors or Antigens on Abnormal Endothelium

The Examiner alleges that the indefinite number of undisclosed antigen, receptor or ligand makes it unpredictable whether the undisclosed antigens, receptors or ligands are expressed on the neovasculature or abnormal endothelium. The application clearly teaches that the antigen, receptor or ligand encompassed by the claims are present on abnormal endothelium (paragraph [014]). The "function" of antigens, receptors or ligands on abnormal endothelium is to allow selective binding or precise targeting of the photo-sensitizing compound to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are bindable to endothelial receptors and antigens (see paragraphs [014] and [032]). Selecting antigens, receptors or ligands that are not expressed on abnormal endothelium would defeat their function as targeting agents to abnormal endothelium. It is respectfully submitted that one of skill in the art would not select antigens, receptors or ligands that are not expressed on abnormal endothelium as targeting agents, and thus it is predictable that the selected antigens, receptors or ligands **are** expressed on the neovasculature or abnormal endothelium.

CONCLUSION

In light of the scope of the claims, the teachings in the specification, the

require undue experimentation for a person of skill in the art to select a targeted photosensitizing compound to practice a method of photodynamic therapy to treat neovascular disease of the eye as claimed; or to select a binding pair that includes an antibody, an antigen, a ligand, or a receptor specific for abnormal endothelium, and binding one member of the binding pair to a targeted photosensitizing compound to practice a method of photodynamic therapy to treat neovascular disease of the eye as claimed. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REBUTTAL TO EXAMINER'S ARGUMENTS

Protein Structure

The Examiner alleges that without the guidance as to the structure of the protein such as the antigen, the receptor, or the ligand, it is allegedly unpredictable which undisclosed antigen, receptor and ligand would be effective for targeting any photosensitizing compound to abnormal endothelium. The applicant respectfully disagrees. As discussed above, none of claims 1-6, 11-12, 16-24 or 36 are directed to any specific antigen, receptor or ligand. Thus, the overall structure of the antigen, receptor or ligand is not relevant to patentability. Further, the applicant respectfully submits that the claimed antigens, receptors or ligands are not restricted to protein. It is well known to those skilled in this art that antigens and ligands are not limited to proteins, but include carbohydrates, such as the blood group antigens (see Janeway *et al.*, Immunobiology, 3rd edition, 1997, page 2.12), glycans, lipopolysaccharides or peptides (Janeway *et al.*, pages 3:8, 3:9 and 9:11).

It is respectfully submitted that no evidence is provided to support the Examiner's position that "without the guidance as to the structure of the protein such as the antigen, the receptor, or the ligand it is allegedly unpredictable

[illegible] photosensitizing compound [illegible] abnormal endothelium [illegible]

provided to show that antigens, receptors and ligands of abnormal endothelium are only protein. The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well- known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The facts of which the Examiner is taking notice are conclusory and are not capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

Hence, if this position is maintained, the Examiner must provide a reference supporting this position.

Antibodies Directed to Proteins

The Examiner alleges that antibody binding specificity differs depending on how the antibodies are elicited. The Examiner cites to Kuby *et al.* for the proposition that antibody binding specificity depends on whether a full-length polypeptide or a peptide fragment is used as the immunogen to elicit the antibody. The applicant submits that while the structure of an immunogen may determine specificity during antibody formation (such as using a peptide versus a full-length polypeptide as alleged by the Examiner), antibodies raised against a given antigen can cross-react with a partially related antigen which bears one or more identical or similar immunodeterminants (Roitt, *Essential Immunology*, pages 14-15, 1984). It is respectfully submitted that the instant claims are not directed to generation of antibodies. The specification teaches selecting an antibody that demonstrates the ability to combine specifically or has a high degree of affinity for abnormal endothelium (see paragraph [0211]), so that a

selectively bind to abnormal endothelium.

Entitlement to broader claims than only the disclosed conditions

The Office Action alleges that the claims are enabled only for what applicant has specifically exemplified. Applicant respectfully submits that all the possible embodiments for "photosensitizers," "binding pair," "endothelial receptors," "endothelial ligands," "endothelial antigens," "antibodies that selectively bind to abnormal endothelium," and "neovascular disease of the eye" known to one of skill in the art are contemplated to be within the scope of claims. The specification discloses exemplary embodiments of each. Numerous alternate embodiments are known to those of skill in the art, as evidenced by the references made of record and discussed above.

A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology, and the Patent Office may not limit all claims to the specific examples. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973). Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The specification recites that the claimed subject matter is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovasculature tissue; and illuminating the neovasculature tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue, where a combination of an intensity of light used for the step of illuminating and a duration of illumination are selected to produce a total

Applicant notes that the Examiner states that the exemplified steps **are enabled** in the specification (paper number 17, pages 3-4). The mere fact that the precise steps of the embodiment exemplified in the specification are not recited in the claims does not provide sufficient reason to hold the claims non-enabled. The enablement requirement of 112, first paragraph does not require that the claims recite specific elements for "photosensitizing compound" or "binding pair" or "endothelial antigen" or "endothelial ligand" or a specific "antibody that selectively binds to abnormal endothelium" or even that the specification recite specific elements for all circumstances, when such elements can be readily determined by one skilled in the art using the teachings of the specification. As discussed in detail above, various "photosensitizing compounds" and "binding pairs" and "endothelial antigens" and "endothelial ligands" and "antibodies that selectively bind to abnormal endothelium" are known in the art. Reciting precise elements in the claims would be unduly limiting and should not be required.

In this instance, applicant is providing a general method of photodynamic therapy to treat neovascular disease of the eye. To limit the claims to specific elements for "photosensitizing compound" or "binding pair" or "endothelial antigen" or "endothelial ligand" or a specific "antibody that selectively binds to abnormal endothelium" would permit those of skill in the art to practice the claimed method, but avoid infringement, merely by substituting different elements to achieve the same outcome, which could be readily identified using the methods described in the specification and known in the art. Further, it is contrary to the public policy and constitutional mandate that underlie the U.S. patent system and upon which the U.S. patent laws are based to require Applicant to limit the claims to only the specifically exemplified embodiments.

> "The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires [illegible] the specification [illegible] and [illegible]
> 306 F.2d 494, 134 USPQ 301, at 304.

Therefore, in light of the scope of the claims, which are tailored to the scope of the disclosure, the extensive description in the application, the presence of working examples and the high level of skill of those in this art, it would not require undue experimentation to practice the methods as claimed. It is respectfully submitted that the rejections of claims 1-6, 11-12, 16-24 and 36 under 35 U.S.C. § 112, first paragraph, are overcome by the above remarks and/or amendments and must be withdrawn.

REJECTION OF CLAIMS 1-6, 11-12, 16-24 and 36 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-6, 11-12, 16-24 and 36 are rejected under 35 U.S.C. 112, first paragraph because the Examiner alleges that the specification only provides a written description for a method to treat neovascular disease of the eye using verteporfin conjugated to L19 antibody that binds to the ED-B domain of fibronectin, and benzoporphyrin conjugated to VEGF, that selectively binds to abnormal endothelium that lines or composes neovascular tissue. The Examiner contends that there is insufficient written description about the structure and function of any photosensitizing compound, the binding specificity of any antibody, or the targeted antigen. The Examiner alleges that the specification discloses only one ligand (the ED-B domain of fibronectin), one specific binding pair (VEGF that binds to the VEGF receptor), one antibody (antibody to the ED-B domain of fibronectin), and only two photosensitizing compounds (verteporfin and benzoporphyrin), and thus alleges that the specification fails to provide a representative number of species to describe the genus.

This rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96

[illegible] may be met by either an express or implicit disclosure

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] *Vas-Cath, Inc. v. Mahurkar*, at 1115, quoting *In re Ruschig*, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of

THE CLAIMS

The claims are discussed above.

ANALYSIS

The Examiner alleges that, with the exception of the specific ligands recited in claim 13, the specification discloses as species of the claimed genera only one ligand (ED-B of fibronectin), one specific binding pair (VEGF that binds to a VEGF receptor), one antibody (antibody to the ED-B of fibronectin) and only two photosensitizing compounds (verteporfin and benzoporphyrin), and alleges that such a disclosure is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera.

First, it is noted that the original claims are part of the specification; hence, the genus including the specific ligands of claim 13 is disclosed in the specification. Second, applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied. The analysis for compliance with the written description requirement where claims are directed to a genus is as follows:

a) does the art indicate substantial variation among the species within the genus?

b) are there a representative number of examples explicitly or implicitly disclosed in the application as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species?

The claimed "genera"

As discussed above and below, claim 1 is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovasculature tissue. Thus, "photosensitizing compound" represents a genus. Claim 11 and its dependent

compound is bound to a first member of a binding pair, and thus, binding pair

represents a genus. The "genus" encompasses the exemplified species and other species that are similar in function to the exemplified species.

Photosensitizing Compound

a) There is no indication in the art that there is substantial variation among members of the genus. The claims are directed to methods of photodynamic therapy that include a photoreactive chemical compound that homes to one or more types of selected cells and, when contacted by radiation, absorbs light, which results in impairment or destruction of the target cells (see paragraph [036]). The specification teaches that those of skill in the art recognize common elements among photosensitizing compounds. For example, the specification teaches that the chemical is nontoxic to the subject prior to irradiation or in its photodegraded form, and absorbs light in a range of 500-1100 nm (paragraph [036]), whereby the chemical is activated and generates singlet oxygen and other reactive species that have biological effects resulting in damage to the endothelial membranes and ultimately to clotting the neovasculature (see paragraph [005]). Thus, the art recognizes that there are common conserved elements among photosensitizing compounds.

b) The specification provides a representative number of examples explicitly (17 by compound family, including porphyrins, purpurin, chlorins, bacteriochlorophylls, phthalocyanines, merocyanines, psoralens, benzoporphyrin derivatives, porfimer sodium, δ-aminolevulinic acid, pyropheophorbides, texaphyrins, verteporfin, indocyanine green, methylene blue, and toluidine blue and two by specific tradename (PHOTOPHRIN® and FOSCAN®) and implicitly by defining the properties requisite for activity in photodynamic therapy. The applicant provides specific working examples that include three different photosensitizing compounds (verteporfin [054], benzoporphyrin [058], and texaphyrin [061]). Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of

Binding Pair

The subject matter of claim 11 and its dependent claims is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes a binding pair that allows the selective binding of the photosensitizing compound to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens (see paragraph [032]).

One member of the binding pair is conjugated to the photosensitizing compound and combines with its counterpart to target the photosensitizing compound. The binding pair can include as one member of the binding pair a receptor present on abnormal endothelium, a ligand bindable to receptor present on abnormal endothelium, an antigen present on abnormal endothelium, an antibody bindable to antigen present on abnormal endothelium, and an antibody bindable to a receptor present on abnormal endothelium.

a) There is no indication in the art that there is substantial variation among members of the claimed genus. The specification teaches that the ligand can be any molecule or compound that binds specifically to upregulated or abnormal blood vessel walls (see paragraph [042]). Thus, one of skill in the art would recognize one common element of the claimed ligands is that they bind specifically to upregulated or abnormal blood vessel walls. The specification also teaches that the receptor preferably is mainly or only found on the abnormal blood vessel wall (see paragraph [042]). Thus, one of skill in the art would recognize one common element of the claimed receptors is that they are mainly or only found on the abnormal endothelium. For example, as discussed above, at the time the application was filed, many endothelial receptors were known, including VEGF receptors, $\alpha v\beta 3$ integrins, the extra-domain B (ED-B) of fibronectin, endothelial-leukocyte adhesion molecule (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and

integrins, LFA-1 for ICAM-1 and VLA-4 for VCAM-1. The specification also teaches that the binding pair can include antibodies that are bindable to endothelial receptors or to endothelial antigens (see paragraph [032]). Thus, one of skill in the art would recognize one common element of the claimed antibodies is that they are specific for or have a high degree of affinity for ligands that bind to upregulated or abnormal blood vessel walls or to receptors that are mainly or only found on abnormal endothelium. Thus, the art recognizes that there are common conserved elements among the receptors and/or antigens and/or ligands and/or antibodies of the binding pair capable of binding to target endothelium.

b) The specification provides a representative number of examples of receptors, antigens, ligands and antibodies of the binding pair explicitly (including VEGF, VEGF receptor, $\alpha v\beta 3$ integrin receptor, CEA antigen, antibody to the extra-domain B of fibronectin, such as L19, antibody to $\alpha v\beta 3$, such as LM609, antibody to CEA, and bispecific antibody construct that is a combination of ligand and receptor (see paragraphs [021], [043], [044] and [061]) and implicitly (such as antibodies and antibody fragments that bind to abnormal vascular endothelial receptors, and antibodies and antibody fragments that bind to upregulated vascular endothelial receptors). The specification defines the properties requisite for activity (binding to an upregulated endothelial receptor or an endothelial receptor found on an abnormal blood vessel wall). The applicant provides specific working examples that include four different ligands (ED-B of fibronectin [054], VEGF [058], $\alpha v\beta 3$ integrin [061], and carcinoembryonic antigen [063]) and 2 receptors (VEGF receptor [059] and $\alpha v\beta 3$ integrin [061]). Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed.

REJECTION OF CLAIMS 1, 11, 23 and 24 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1, 11, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the Examiner alleges that (1) the recitation "non-laser light source" in claims 23 and 24 lacks proper antecedent basis in claim 1, and (2) the recitation "component" in claim 11 is ambiguous and indefinite because the specification does not define the specific component of any binding pair, and thus the metes and bounds of the claimed subject matter cannot be ascertained.

This rejection is respectfully traversed.

Claim 1

The Examiner provides no basis for the rejection of claim 1. Applicant respectfully requests that the Examiner identify the basis of the rejection of claim 1 under 35 U.S.C. 112, second paragraph or withdraw the rejection.

Claim 11

Claim 11 is rejected because the recitation "component" is alleged to be ambiguous and indefinite. It is respectfully submitted that amendment of claim 11 herein obviates this rejection.

Claims 23 and 24

Claims 23 and 24 are rejected because the recitation "non-laser light source" allegedly lacks proper antecedent basis. It is respectfully submitted that amendment herein of claims 23 and 24 to correct the dependency so that they depend from claim 2 instead of claim 1 obviates this rejection.

THE REJECTION OF CLAIMS 1, 3, 4, 6, 18-22 and 36 UNDER 35 U.S.C. §102(b)

Claims 1, 3, 4, 6, 18-22 and 36 are rejected under 35 U.S.C. § 102(b) as anticipated by Strong *et al.* (U.S. Patent No. 5,756,541) because Strong *et al.* allegedly discloses a method to treat neovascular disease of the

compound such as a chlorin and green porphyrin coupled to a specific binding ligand such as an antibody that binds to the target ocular tissue.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

The claims are discussed above.

Disclosure of Strong *et al.*

Strong *et al.* discloses a photodynamic therapy of the eye to reduce unwanted neovasculature, especially neovasculature of the choroid (col. 2, lines 1-3). Strong *et al.* discloses that its green porphyrins strongly interact with lipoproteins (col. 3, lines 53-56). Strong *et al.* discloses coupling the photo-sensitizer to a target-specific ligand such as an antibody or an immunologically

discloses one method during the irradiating treatment can only, indeed be

preferably varies from about 50-200 J/cm^2 (col. 4, lines 56-59), and that irradiance varies from about 150-900 mW/cm^2 (col. 4, lines 60-64). Strong *et al.* discloses that the duration of light irradiation depends on the fluence desired (col. 5, lines 5-8). Strong *et al.* discloses that its treatment results in mild retinal whitening in some cases (col. 5, lines 10-13).

Differences between the claimed subject matter and the disclosure of Strong *et al.*

Strong *et al.* does not disclose a method to treat neovascular disease of the eye that includes as a step selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Strong *et al.* does not disclose any significance of the parameters of light intensity and/or duration of irradiation, nor is there any disclosure on the selection of a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target tissue destruction without damage to non-target tissue. Strong *et al.* does not disclose that its treatment method is effective in treating target tissue without damaging the healthy tissue, and provides little discussion on the effects of its treatment methods on healthy tissues, but discloses that mild retina whitening occurs. Hence, Strong *et al.* does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Thus, Strong *et al.* does not disclose every element of claim 1. Because Strong *et al.* does not disclose every element of claim 1, Strong *et al.* does not anticipate claim 1. Because claims 3, 4, 6, 18-22 and 36 depend from claim 1,

Rebuttal to Examiner's Arguments

Claims 19-21

The Examiner alleges that Strong *et al.* discloses illuminating the photoactive agent for about 1 minute to about 2 hours, and cites col. 5, lines 2-4 to support the allegation. The applicant respectfully disagrees. Strong *et al.* discloses that

> [t]he optimum time following photoactive agent administration **until** light treatment can also vary widely depending on the mode of administration, the form of administration and the specific ocular tissue being targeted. Typical times after administration of the photoactive agent range from about 1 minutes to about 2 hours, preferably about 5-30 minutes, and more preferably 10-25 minutes.

[emphasis added] (col. 4, line 65 through col. 5, line 4). The cited section discloses the interval between administration of the photoactive agent and the administration of light, and does NOT disclose the time for illumination as alleged by the Examiner. Strong *et al.* discloses that for an irradiance of 600 mW/cm^2, a fluence of 50 J/cm^2 requires 90 seconds of irradiation and 150 J/cm^2 requires 270 seconds of irradiation (col. 5, lines 5-8).
Because Strong *et al.* discloses a fluence between 50-200 J/cm^2, Strong *et al.* does not disclose illuminating the photosensitized neovasculature for at least 20 minutes, or at least 1 hour, or at least 24 hours.

Claim 22

Claim 22 is rejected because the Examiner alleges that Strong *et al.* discloses an irradiance that varies from about 150 to 900 mW/cm^2 and a total fluence of 50 to 150 J/cm^2. Applicant respectfully submits that claim 22 is directed to the method of claim 1 where the neovascular tissue is treated with a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2. Strong *et al.* does not disclose a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2. There is no overlap in fluence

THE REJECTION OF CLAIMS UNDER 35 U.S.C. §103(a)

All claims are rejection under 35 U.S.C. §103(a) over various references. Before addressing the specific grounds of rejection, the Examiner's attention is directed to co-owned Patent No. 6,602,274, based on U.S. application Serial No. 09/271,575, noted above. The issued claims in the co-owned patent, which has the same inventive entity, are directed to a generic method of photodynamic therapy. For example, claim 1 recites:

> 1. A method for administering a photodynamic therapy to a target tissue or composition in a mammalian subject, comprising the steps of:
>
> (a) administering to the subject a therapeutically effective amount of a targeted photoreactive compound having a characteristic light absorption waveband, said targeted photoreactive compound selectively binding with the target tissue or composition, but not binding with a non-target tissue or composition;
>
> (b) transdermally irradiating at least a portion of the mammalian subject in which the target tissue or composition to which the targeted photoreactive compound has bound is disposed, with light having a waveband corresponding at least in part to the characteristic light absorption waveband of said targeted photoreactive compound; wherein
>
> the intensity of the light used for the step of transdermally irradiating and the duration of irradiation have been selected such that the target tissue or composition is destroyed and the non-target tissue or composition through which the light passes remains undamaged.

This claim is presumptively novel and unobvious, since the patent has issued. The present claims include the recitation:

> . . .wherein
>
> a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

REJECTION OF CLAIMS 1, 2, 11 and 12 UNDER 35 U.S.C. §103(a)

Claims 1, 2, 11 and 12 are rejected under 35 U.S.C. §103(a)

Br. J. Ophthalmol. 82: 561-568, 1998), Blaauwgeers *et al.* (*Am. J. Pathology*

155(2): 421-428, 1999), Klyashchitsky *et al.* (*J of Controlled Release 29(1-2)*: 16-16, 1994) and Prewett *et al.* (*Cancer Res 59*: 5209-18, 1999) because although Strong *et al.* does not teach non-laser light (claim 2), or binding the photosensitizer to a first member of a binding pair (claim 11), or incorporation of the targeted photosensitizing compound into a liposomal preparation (claim 12), Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* allegedly cure these defects.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553.

THE CLAIMS

The claims are discussed above.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teachings of Strong *et al.* are discussed above.

Boulton *et al.*

Boulton *et al.* teaches that VEGF was generally absent from normal retina and that staining of tissue using anti-VEGF antibody showed VEGF in most diabetic tissue, but that this was dependent on both the specificity of the antibody used and the category of the tissue (page 561, col. 1., lines 24-29). Boulton *et al.* teaches that some anti-VEGF antibodies also associated with extravascular components of the inner retina (page 561, col. 1, lines 33-35). The reference teaches that VEGF staining correlated with active neovascularization and that VEGF may play a role in diabetic retinopathy (page 566, col. 1, lines 48-56). Boulton *et al.* teaches laser photocoagulation (page 567, col. 1, lines 26-31).

Boulton *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a targeted photosensitizing compound that selectively binds to abnormal endothelium. Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Blaauwgeers *et al.*

Blaauwgeers *et al.* teaches that the retinal pigment epithelium monolayer is involved in the pathogenesis of choroidal neovascularization such as in age-related macular degeneration (page 421, col. 2, lines 13-16). Blaauwgeers *et al.* teaches that VEGF plays a role in normal eye functioning and that up-regulated

3-9). The reference teaches that defects in the retinal pigment epithelium monolayer could lead to misdirection of secreted VEGF and subsequent classical subretinal neovascularization (page 428, col. 1, lines 1-4).

Blaauwgeers *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a targeted photosensitizing compound that selectively binds to target endothelium. Blaauwgeers *et al.* does not teach or suggest illuminating neovascular tissue to activate a photosensitizing compound, nor does the reference teach or suggest coherent or non-coherent light for such illumination. Blaauwgeers *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Klyashchitsky *et al.*

Klyashchitsky *et al.* teaches that photodynamic therapy is based on the ability of porphyrins and some other photosensitizers to accumulate preferentially in tumor cells and to generate singlet oxygen when activated by visible light (page 1, abstract). Klyashchitsky *et al.* teaches targeted photosensitizers using targeting moieties having high affinity to the tumor-associated antigen or receptor (page 2, col. 2, lines 21-26). Klyashchitsky *et al.* teaches that such targeting moieties include monoclonal antibodies, liposomes, low density lipoproteins and lectins (page 2, col. 1, lines 24-33).

Klyashchitsky *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a targeted photosensitizing that selectively binds to target endothelium. Klyashchitsky *et al.* does not teach or suggest illuminating neovascular tissue to activate a photosensitizing compound, nor does the reference teach or suggest coherent or non-coherent light for such illumination. Klyashchitsky *et al.* does

such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Prewett *et al.*

Prewett *et al.* teaches that tumor angiogenesis is mediated by tumor-secreted growth factors that interact with their surface receptors expressed on endothelial cells, and that VEGF and the VEGF receptor play a role in vascular permeability and tumor angiogenesis (page 5209, col. 1, lines 1-5). Prewett *et al.* teaches that anti-VEGF receptor antibody treatment of tumors results in decreased microvessel density, tumor cell apoptosis, decreased tumor cell proliferation and extensive tumor necrosis (page 5209, col. 1, lines 23-29). The reference teaches that VEGF and VEGF receptors are implicated in angiogenesis that occurs in many human solid tumors (page 5209, col. 2, lines 25-27), and that blocking the VEGF receptor with anti-VEGF receptor antibodies inhibits angiogenesis (page 5214, col. 2, lines 9-12). Prewett *et al.* teaches that neutralizing soluble VEGF receptor or Flk-1/KDR kinase inhibitors inhibited angiogenesis and tumor growth (page 5209, col. 2, lines 33-37).

Prewett *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a targeted photosensitizing compound that selectively binds to target endothelium. Prewett *et al.* does not teach or suggest illuminating neovascular tissue to activate a photosensitizing compound, nor does the reference teach or suggest coherent or non-coherent light for such illumination. Prewett *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case

The combination of teachings of Strong *et al.* with the teachings of Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* does not result in the instantly claimed methods.

Independent claim 1 and claims dependent thereon include as subject matter selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Nowhere in Strong *et al.* is it taught or suggested that, in a method of photodynamic therapy using a targeted photosensitizer compound, the parameters of irradiation intensity and irradiation duration can be varied and selected to achieve destruction of neovascular tissue without damage to a non-target tissue through which the light passes during irradiation. Strong *et al.* provides little, if any, guidance on the combination of light intensities and duration of irradiation to be used in therapeutic methods involving photosensitizing compounds. There is no teaching or suggestion in Strong *et al.* that, in conducting photodynamic therapy, there are combinations of the parameters of light intensity and duration of irradiation that can be selected, which, when used in conjunction with a targeted photosensitizer compound, provide a total fluence that achieves destruction of the target tissue without damage to a non-target tissue.

Boulton *et al.* does not cure these defects. Boulton *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, and thus Boulton *et al.* contains no teaching or suggestion of the parameters of the intensity or duration of light used for photodynamic therapy. The combination of the teachings of Strong *et al.* and Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Boulton *et al.* [illegible]

of the teachings of Strong *et al.* and Boulton *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Blaauwgeers *et al.* does not cure these defects. Blaauwgeers *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, and thus Blaauwgeers *et al.* contains no teaching or suggestion of the parameters of the intensity or duration of light used for photodynamic therapy. The combination of the teachings of Strong *et al.* and Blaauwgeers *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Blaauwgeers *et al.* teaches that the loss of polarity of VEGF production may play a role in the pathogenesis of choroidal neovascularization, the combination of the teachings of Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Klyashchitsky *et al.* does not cure these defects. Klyashchitsky *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Blaauwgeers *et al.* teaches targeted photosensitizers, the combination of the teachings of Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* and Klyashchitsky *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Prewett *et al.* does not cure these defects. Prewett *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the

eaches that blocking the VEGF receptor with anti-VEGF receptor antibodies

inhibits angiogenesis, the combination of the teachings of Strong *et al.*, Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* does not teach or suggest every element of claim 1.

Thus, the combination of the teachings of Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* and Klyashchitsky *et al.* and Prewett *et al.* does not result in the subject matter of claims 1, 2, 11 and 12. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The Rejection over Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* and Klyashchitsky *et al.* and Prewett *et al.* is Based on Improper Use of Hindsight.

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. *In re Laskowski*, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

It is only through hindsight analysis that one can imbue the prior art with the various elements of the claimed subject matter. In this instance, it appears that the Examiner has scoured the prior art teachings using the instant application as a guide and is picking and choosing the elements "targeted photosensitizer," "VEGF receptors," "endothelial" and "neovascularization" from the various references to combine them as claimed in the instant application.

Further, there are deficiencies in the teachings of the cited art, whether taken alone or in combination. The combination of cited references does not result in the instantly claimed methods. Nothing in the prior art teaches or suggests a method to treat neovascular disease of the [illegible] abnormal endothelium and selecting a combination of an intensity of light for

illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. As noted above, it is improper to use hindsight or the application at issue to combine the references to produce the claimed subject matter. It is the instant Applicant who discovered the value of selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. In this instance, the Examiner is relying on teachings in the instant application as a guide. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness. It is respectfully submitted that the rejection of claims 1, 2, 11 and 12 under 35 U.S.C. § 103(a) as unpatentable over Strong *et al.* in view of Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* is overcome and should be withdrawn.

REJECTION OF CLAIMS 1, 16 and 17 UNDER 35 U.S.C. §103(a)

Claims 1, 16 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strong *et al.* (U.S. Patent No. 5,756,541) in view of Thorpe *et al.* (U.S. Patent No. 6,051,230) because Strong *et al.* allegedly teaches every element of the claimed subject matter except a targeted photosensitizing compound that is bound to a bi-specific antibody, but Thorpe *et al.* allegedly cures this defect. The Examiner contends that Thorpe *et al.* teaches various antibodies to VEGF and methods of making bi-specific antibodies, and that bi-specific antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature through recognition of VEGF or other receptors on endothelial cells. The Examiner contends that it would have been obvious to substitute the bi-specific antibodies of Thorpe *et al.* for the antibody taught in Strong *et al.* for targeting the photosensitive compound to neovasculature tissue in the eye.

This rejection is respectfully traversed.

[illegible]

the relevant law is discussed above.

THE CLAIMS

The claims are discussed above.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teachings of Strong *et al.* are discussed above.

Thorpe et al.

Thorpe *et al.* teaches the use of immunological reagents to target therapeutic or diagnostic agents to tumor-associated vascular endothelial cells, alone or in combination with the direct targeting of tumor cells (col. 4, lines 11-16). Thorpe *et al.* teaches various antibodies directed to VEGF (col. 83, line 11 through col. 84, line 36). Thorpe *et al.* teaches bi-specific antibodies having specificity for the targeted tumor cell antigen on the one hand and the targeted activating molecule on the other (col. 29, lines 25-30). Thorpe *et al.* teaches that bi-specific antibodies recognize a selected tumor cell surface antigen and a selected cytokine activating antigen on the surface of a selected leukocyte cell type such that once introduced into the bloodstream, the bi-specific construct will bind to tumor cells and cross-link the tumor cells with the leukocyte cells (col. 12, lines 16-44).

Thorpe *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a targeted photosensitizing compound that selectively binds to abnormal endothelium. Thorpe *et al.* does not teach or suggest administering a photoreactive compound that selectively binds to abnormal endothelium that lines or composes neovasculature tissue. Thorpe *et al. et al.* does not teach or suggest illuminating neovascular tissue to activate a photosensitizing compound. Thorpe *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following.

The combination of teachings of Strong *et al.* with the teachings of Thorpe *et al.* does not result in the instantly claimed methods.

Independent claim 1 and claims dependent thereon include as subject matter selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. As discussed above, nowhere in Strong *et al.* is it taught or suggested that, in a method of photodynamic therapy using a targeted photosensitizer compound, the parameters of irradiation intensity and irradiation duration can be varied and selected to achieve destruction of neovascular tissue without damage to a non-target tissue through which the light passes during irradiation.

Thorpe *et al.* does not cure this defect. Thorpe *et al.* does not teach or suggest photodynamic therapy or selecting the parameters of the intensity or duration of light used for photodynamic therapy. The combination of the teachings of Strong *et al.* and Thorpe *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Thorpe *et al.* teaches bi-specific antibodies, the combination of the teachings of Strong *et al.* and Boulton *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

It is respectfully submitted that the rejection of claims 1, 16 and 17 under 35 U.S.C. § 103(a) as unpatentable over Strong *et al.* in view of Thorpe *et al.* is overcome by the above remarks and should be withdrawn.

REBUTTAL TO EXAMINER'S ARGUMENTS

Bispecific Antibody Construct

The Examiner alleges that Thorpe *et al.* teaches a bi-specific antibody construct that includes both a ligand component and a receptor component. The applicant respectfully disagrees. Thorpe *et al.* teaches (col. 12, lines 16-20)

> [b]ispecific antibodies useful in the practice of this aspect of the invention, therefore, will have a dual specificity, recognizing a selected tumor cell surface antigen on the one hand, and, on the other hand, recognizing a selected "cytokine activating" antigen on the surface of a selected leukocyte cell type.

Thus, the bi-specific antibody construct of Thorpe *et al.* includes two **ligand** components (each of which recognize a different cell surface antigen). Thorpe *et al.* does not teach or suggest a bi-specific antibody construct that includes both a ligand component and a receptor component.

The Examiner also alleges that claim 46 of Thorpe *et al.* particularly teaches a bispecific antibody construct that includes both a ligand component and a receptor component. The applicant respectfully disagrees. Claim 46 depends from claim 40, which is directed to a combination of a first conjugate including a first antibody and a second conjugate including a second antibody. Neither claim 40 nor claim 46 teaches or suggests a bispecific antibody construct that includes **both** a ligand component and a receptor component. Therefore, Thorpe *et al.* does not teach or suggest a bi-specific antibody construct that includes both a ligand component and a receptor component.

REJECTION OF CLAIMS 1, 23 and 24 UNDER 35 U.S.C. §103(a)

Claims 1, 23 and 24 are rejected under 35 U.S.C. §103(a) as being unpatentable over Strong *et al.* (U.S. 5,756,541) in view of Prasad *et al.* (US 5,912,257) because Strong *et al.* allegedly teaches every element of the claimed subject matter except a non-laser light source such as a light emitting diode or ambient light, but Prasad *et al.* allegedly cures this defect. The Examiner alleges

herein light sources to activate a photoreactive and alleges that

skill in the art would substitute the styryl dye of Thorpe *et al.* for the photosensitizing compound of Strong *et al.* and use a non-laser light source to activate the dye.

This rejection is respectfully traversed.

RELEVANT LAW

The relevant law is discussed above.

THE CLAIMS

The claims are discussed above.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teaching of Strong *et al.* are discussed above.

Prasad *et al.*

Prasad *et al.* teaches a matrix material and a styryl compound dispersed therein (col. 10, lines 41-43) where the styryl compounds have greater two-photon absorption cross-sections and stronger upconversion fluorescence emission than organic dyes (col. 11, lines 57-61). Prasad *et al.* teaches a method for converting infrared radiation to visible light (col. 41, lines 12-17). Prasad *et al.* teaches that its methods are well suited for use as an aid in aligning infrared laser beams, such as those produced by alexandrite, ruby, Ti-sapphire, helium-neon and GaAlAs and InGaAs diode lasers (col. 38, lines 1-8). Prasad *et al.* teaches PDT methods for treating head, neck, pancreatic, bronchial, cervical, esophageal or colon cancers and to dissolve blood plaques (col. 55, lines 59-66). Prasad *et al.* teaches PDT methods to treat acne, athlete's foot, warts and psoriasis (col. 56, lines 2-5).

Prasad *et al.* does not teach or suggest methods to treat neovascular disease of the eye. Prasad *et al.* does not teach or suggest using a targeted photosensitizing compound that selectively binds to abnormal endothelium. Prasad *et al.* does not teach or suggest selecting a combination of an intensity

that the neovascular tissue is destroyed and the non-target tissue (neural tissue

the light passes remains undamaged. Prasad *et al.* does not teach or suggest a light emitting diode as a non-coherent light source. Prasad *et al.* does not teach or suggest using ambient light as a non-coherent light source to activate its dye.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following.

The combination of teachings of Strong *et al.* with the teachings of Prasad *et al.* does not result in the instantly claimed methods.

Independent claim 1 and claims dependent thereon (for example, claims 2, 23 and 24) include as subject matter selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. As discussed above, Strong *et al.* does not teach or suggest that the parameters of irradiation intensity and irradiation duration can be varied and selected to achieve destruction of neovascular tissue without damage to a non-target tissue through which the light passes during illumination.

Prasad *et al.* does not cure this defect. Prasad *et al.* does not teach or suggest selecting the parameters of the intensity or duration of light used for photodynamic therapy to achieve destruction of neovascular tissue without damage to a non-target tissue through which the light passes. Thus, the combination of the teachings of Strong *et al.* and Prasad *et al.* does not teach or suggest every element of claims 1, 2, 23 and 24. Therefore, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REBUTTAL TO EXAMINER'S ARGUMENTS

Light Emitting Diode as Non-Coherent Light Source

The Examiner alleges that Prasad *et al.* teaches at column 37, lines 64-66 and column 38, line 7 a light emitting diode as a non-coherent light source. The

> [t]he method of the present invention can be used to detect any type of high intensity infrared radiation in the range from 700 to 1300 nm, including coherent, incoherent, polarized, pulsed laser, continuous laser, and diffluse [*sic*] infrared radiation. Because of the high intensities associated with pulsed laser radiation, the methods of the present invention are particularly well suited for detecting radiation from these sources. In particular, the infrared detector is envisaged as an aid in aligning infrared laser beams, such as those produced by, for example, Ti-sapphire, Ruby, Alexandrite, Helium-Neon, GaAlAs and InGaAs diode, Nd-YLF, Nd-glass, and Nd-YAG lasers.

Thus, Prasad *et al.* teaches using its infrared detector to align GaAlAs and InGaAs diode lasers. Nowhere does Prasad *et al.* teach or suggest a light emitting diode as a non-coherent light source to activate a photosensitizer.

Ambient Light as Non-Coherent Light Source

The Examiner alleges that Prasad *et al.* teaches at column 38, lines 59-61 using ambient light as a non-coherent light source to activate its dye. The applicant respectfully disagrees. Prasad *et al.* teaches (col. 38, lines 53-61 that

> The method comprises detecting infrared radiation intensity using the method provided therefor by the present invention at various locations potentially exposed to an infrared laser beam and then correlating the infrared radiation intensity detected at the various locations to the cross-sectional intensity profile of the infrared laser beam. As in the previous detection methods, the infrared intensity is preferably detected visually by evaluating the intensity of emitted visible light.

The cited section of the reference teaches use of an infrared laser to excite the dye of Prasad *et al.* Thus, the reference teaches using **coherent light** to activate its dye compound. Prasad *et al.* further teaches detecting the infrared intensity of the laser by evaluating the intensity of the visible light emitted from the dye due to the excitation caused by the infrared laser. Thus, Prasad *et al.* does not teach or suggest using ambient light as a non-coherent light source to activate

In view of the above, reconsideration and allowance of this application is respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: JAMES C. CHEN

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Tim Chettiath

APPENDIX

1. Copies of the Supplemental Information Disclosure Statement, the date-stamped return receipt postcard, and the Transmittal Letter filed on April 8, 2002.

2. Replacement copy of the Form PTO-1449 originally filed April 8, 2002.

3. Roitt, I., *Essential Immunology* (5th edition, 1984), pages 14-15.

4. Janeway *et al.*, *Immunobiology - The Immune System in Health and Disease* (3rd edition, 1997), pages 2:12, 3:8, 3:9, and 9:11.